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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/774,047	02/06/2004	Zhenwei Miao	4056.1066 US1	4991

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EXAMINER	
JARRELL, NOBLE E	

ART UNIT	PAPER NUMBER
1624	

MAIL DATE	DELIVERY MODE
07/23/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/774,047	MIAO ET AL.	
	Examiner	Art Unit	
	Noble Jarrell	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 April 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-69 and 75-88* is/are pending in the application.

4a) Of the above claim(s) *34,48 and 60* is/are withdrawn from consideration.

5)☒ Claim(s) *1-33,35-47,49-59,61-65 and 75-87* is/are allowed.

6)☒ Claim(s) *66-70* is/are rejected.

7)☒ Claim(s) *88* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Arguments

1. The restriction is still deemed proper because variable L changes the core structure of the ring. When variable L is absent, the ring core represents a different structural query than an instance when variable L is any of the other groups. Therefore, the restriction of 1/8/2008 is MADE FINAL.

2. The rejection under 35 U.S.C. 112 1st paragraph has been overcome by the amendment filed 4/16/2008.

3. The claim objections listed in the non-final rejection of 3/20/08 have been overcome by the amendment filed 4/16/08.

4. The rejections 35 U.S.C. 112 2nd paragraph have been overcome by the amendment filed 4/16/08.

5. As a result of the amended claim set, claims 1-33, 49-59, 61-69, and 75-88 are being examined in the current office action. Since claims 34, 38, and 60 contain non-elected subject matter, they are withdrawn from consideration.

Claim Objections

6. Claim 88 is objected to because of the following informalities: it contains non-elected subject matter. Variable L is absent (or a bond). Appropriate correction is required.

Claim Rejections - 35 USC § 112

7. Claims 66-70 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the *in vitro* inhibition of NS4 or NS4A serine protease, does not reasonably provide enablement for *in vivo* inhibition of these proteases. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these

claims. Njoroge et al. (*Accounts of Chemical Research*, **2008,** *41(1)*, 50-59, cited in previous office action) teach that significant challenges exist in development of HCV polymerase inhibition (section titled "Challenges in discovering HCV protease inhibitors", page 52). **This rejection is maintained**.

> The factors to be considered in determining whether a disclosure meets the enablement requirements of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir., 1988). The court in Wands states, "Enablement is not precluded by the necessity for some experimentation, such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue', not 'experimentation'" (*Wands*, 8 USPQ2sd 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations" (*Wands*, 8 USPQ2d 1404). Among these factors are: (1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the relative skill of those in the art; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

Consideration of the relevant factors sufficient to establish a *prima facie* case for lack of enablement is set forth herein below:

(1) The nature of the invention and (2) the breadth of the claims:

The claims are drawn to a method of inhibiting HCV growth through inhibition of NS3 or NS4A protease.

(3) The state of the prior art and (4) the predictability or unpredictability of the art:

Njoroge et al. teach that significant challenges exist in the discovery of HCV polymerase inhibitors and their use *in vivo*. Njoroge et al. discuss several of the challenges associated with treatment of hepatitis C virus. These challenges include: one, the protease has a shallow and solvent-exposed substrate binding region, and the inhibitor binding energy is mainly derived from weak lipophilic and electrostatic interaction; two, a lack of a roust *in vitro* cell culture system and the absence of a convenient small animal

model have hampered the assessment of both *in vitro* and *in vivo* efficacy of any antiviral compounds. In addition, applicants have failed to satisfy these obstacles. In fact, the assays for testing the ability of the compounds are done on cell cultures and not on any animals. Njoroge et al. also teach that compounds with a similar core structure (see compound 7, page 55) are shown to not have an improved pharmacokinetic profile even though the compound works *in vitro* (page 56, column 1).

(6) The amount of direction or guidance presented and (7) the presence or absence of working examples:

The specification has provided guidance for *in vitro* inhibition of NS3 or NS4A protease using compounds of formula I.

However, the specification does not provide guidance for *in vivo* inhibition of NS3 or NS4A protease using compounds of formula I. In examples 215 and 216 of the specification, applicants have shown that protease activity was inhibited *in vitro* through the use of cultured Huh-11-7 and Hub 9-13 cell lines. The HCV RNA of the cells was amplified using PCR. In example 216, only the calculation method describing the calibration of inhibition is described. No guidance is given as to what compounds actually worked. In addition, applicants have not shown a reduction in viral titers *in vivo*.

(8) The quantity of experimentation necessary:
The pharmaceutical art has been known for its unpredictability due to various conflicting pathways, or biological factors that are sometimes genetically unique to individuals. In the instant case, no data is given for evidence that compounds of formula I actually work *in vitro*. Example 215 shows a general procedure to follow. See *Hoffman v. Klaus* 9 USPQ 2d 1657, and *Ex Parte Powers* 220 USPQ 925 regarding types of testing needed to support *in vivo* uses.

Considering the state of the art as discussed by the references above, particularly with regards to claims 66-70 and the high unpredictability in the art as evidenced therein, and the lack of guidance provided in the specification, one of ordinary skill in the art would be burdened with undue experimentation to practice the invention commensurate in the scope of the claims.

Allowable Subject Matter

8. Claims 1-33, 35-47, 49-59, 61-65, and 75-87 contain allowable subject matter.

9. The following is a statement of reasons for the indication of allowable subject matter: Niu et al. (US20080039470, published February 14, 2008) teach example 25 (page 34). In this compound, variable j equals 2, A is *t*-BOC group, G is NH-tetrazole, and W is tetrazole-4-OMe-phenyl. This compound fails to anticipate or render obvious a compound of claim 1 because variable G cannot have a tetrazole ring.

Conclusion

10. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Noble Jarrell whose telephone number is (571) 272-9077. The examiner can normally be reached on M-F 7:30 A.M - 6:00 P.M. EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. James O. Wilson can be reached on (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Noble Jarrell/
Examiner, Art Unit 1624

/James O. Wilson/
Supervisory Patent Examiner, Art Unit 1624